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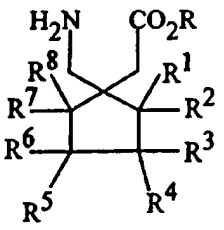
(54) Title: GABAPENTIN ANALOGUES FOR SLEEP DISORDERS



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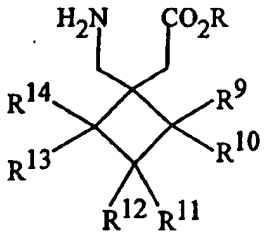

(1A)

(57) Abstract: The invention provides a new use of compounds for formula 1 or 1A or a pharmaceutically acceptable salt thereof. The compounds are useful in the treatment of insomnia and related disorders.

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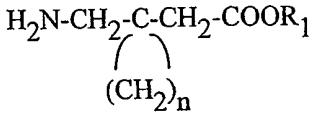
GABAPENTIN ANALOGUES FOR SLEEP DISORDERS

BACKGROUND OF THE INVENTION

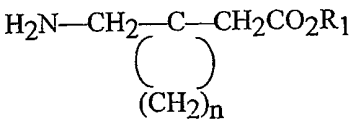
Compounds of formula



wherein R_1 is hydrogen or a lower alkyl radical and n is 4, 5, or 6 are known in United States Patent Number 4,024,175 and its divisional United States Patent Number 4,087,544. The uses disclosed are: protective effect against cramp induced by thiosemicarbazide; protective action against cardiazole cramp; the cerebral diseases, epilepsy, faintness attacks, hypokinesia, and cranial traumas; and improvement in cerebral functions. The compounds are useful in geriatric patients. The patents are hereby incorporated by reference.

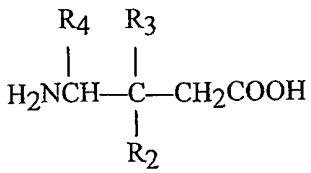
United States Patent Application 09/485,382 filed February 8, 2000, covers compounds of formulas 1 and 1A below. The application discloses various utilities for the compounds. This is incorporated by reference.

Compounds of Formula I



I

wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof and compounds of Formula II



II

hydrogen, methyl, or carboxyl; or an individual enantiomeric isomer thereof; or a pharmaceutically acceptable salt thereof, are useful in the treatment of insomnia (United States Patent Application 60/092166 filed July 9, 1998, which is incorporated here by reference).

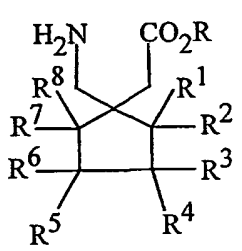
SUMMARY OF THE INVENTION

The instant invention is a method of treating insomnia, that is, difficulty in sleeping or disturbed sleep patterns which leave the perception of insufficient sleep. Insomnia is a common symptom which may be due to several emotional and physical disorders (The Merck Manual, 16th ed., pp 1445-6).

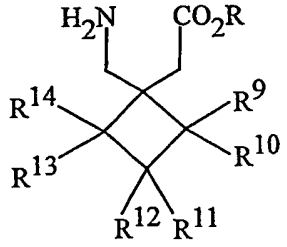
The benefit of using compounds of the invention to treat insomnia is that they are not addictive. Additionally, they have a half-life in the body that is suitable to work during the evening and subsequently clear the body by morning to allow for easy arousal. The compounds can be combined with other agents to enhance the sleep inducing effects. Such agents include melatonin, tryptophan, valerian, passiflora, antihistamines such as diphenydramine hydrochloride or doxylamine succinate, benzodiazepines, and nonbenzodiazepines hypnotics.

Additional advantages of using the compounds of formula 1 and 1A in the present invention include the relatively nontoxic nature of the compounds, the ease of preparation, the fact that the compounds are well-tolerated, and the ease of IV administration of the drugs. The subjects treated with the method of the present invention are mammals, including humans.

The compounds useful in the practice of the invention are those of formulas 1 and 1A



or



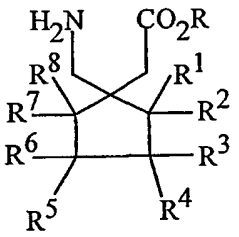
1 1A

wherein R to R^{14} are as defined below.

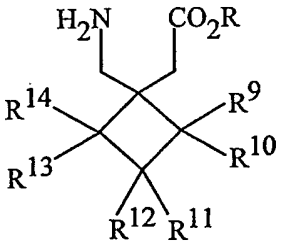
The compounds of the invention and their pharmaceutically acceptable salts and the prodrugs of the compounds are useful in the treatment of insomnia and sleeplessness.

DETAILED DESCRIPTION OF THE INVENTION

The compounds useful in the instant invention and their pharmaceutically acceptable salts are as defined by formulas 1 and 1A



and



1 1A

or a pharmaceutically acceptable salt thereof wherein:

R is hydrogen or a lower alkyl;

R^1 to R^{14} are each independently selected from hydrogen, straight or branched alkyl of from 1 to 6 carbons, phenyl, benzyl, fluorine, chlorine, bromine, hydroxy, hydroxymethyl, amino, aminomethyl, trifluoromethyl, $-CO_2H$, $-CO_2R^{15}$, $-CH_2CO_2H$, $-CH_2CO_2R^{15}$, $-OR^{15}$ wherein R^{15} is a straight or branched alkyl of from 1 to 6 carbons, phenyl, or benzyl, and R^1 to R^8 are not simultaneously hydrogen.

Preferred compounds of the invention are those of Formula I wherein R^1 to R^{14} are selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl straight or branched, phenyl, or benzyl.

More preferred compounds are those of Formula I wherein R^1 to R^{14} are selected from hydrogen, methyl, ethyl, or benzyl.

The most preferred compounds are selected from:

(1α,3α,4α)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid;

(1α,3α,4α)-(1-Aminomethyl-3,4-diethyl-cyclopentyl)-acetic acid;

(1α,3α,4α)-(1-Aminomethyl-3,4-diisopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-ethyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-ethyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-isopropyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-isopropyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

(1α,3α,4α)-(1-Aminomethyl-3,4-di-tert-butyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;

(S)-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-acetic acid;

(S)-(1-Aminomethyl-3,3-diethyl-cyclopentyl)-acetic acid;

(1-Aminomethyl-3,3,4,4-tetramethyl-cyclopentyl)-acetic acid;

(1-Aminomethyl-3,3,4,4-tetraethyl-cyclopentyl)-acetic acid;

(1α,3β,4β)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid;

(1α,3β,4β)-(1-Aminomethyl-3,4-diethyl-cyclopentyl)-acetic acid;

(1α,3β,4β)-(1-Aminomethyl-3,4-diisopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-ethyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-ethyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-isopropyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-isopropyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-tert-butyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-tert-butyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

(1α,3β,4β)-(1-Aminomethyl-3,4-di-tert-butyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;

(R)-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-acetic acid;

(R)-(1-Aminomethyl-3,3-diethyl-cyclopentyl)-acetic acid;

cis-(1-Aminomethyl-3-methyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-ethyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-isopropyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-tert-butyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-phenyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-benzyl-cyclobutyl)-acetic acid;

trans-(1-Aminomethyl-3-methyl-cyclobutyl)-acetic acid;

trans-(1-Aminomethyl-3-ethyl-cyclobutyl)-acetic acid;

trans-(1-Aminomethyl-3-isopropyl-cyclobutyl)-acetic acid;

trans-(1-Aminomethyl-3-tert-butyl-cyclobutyl)-acetic acid;

trans-(1-Aminomethyl-3-phenyl-cyclobutyl)-acetic acid;

trans-(1-Aminomethyl-3-benzyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-ethyl-3-methyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-isopropyl-3-methyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-tert-butyl-3-methyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-methyl-3-phenyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-benzyl-3-methyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-ethyl-3-methyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-isopropyl-3-methyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-tert-butyl-3-methyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-methyl-3-phenyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-benzyl-3-methyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-ethyl-3-isopropyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-tert-butyl-3-ethyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-ethyl-3-phenyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-benzyl-3-ethyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-ethyl-3-isopropyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-tert-butyl-3-ethyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-ethyl-3-phenyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-benzyl-3-ethyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-tert-butyl-3-isopropyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-isopropyl-3-phenyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-benzyl-3-isopropyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-tert-butyl-3-phenyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-benzyl-3-tert-butyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-tert-butyl-3-isopropyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-isopropyl-3-phenyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-benzyl-3-isopropyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-tert-butyl-3-phenyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-benzyl-3-tert-butyl-cyclobutyl)-acetic acid;
(1-Aminomethyl-3,3-dimethyl-cyclobutyl)-acetic acid;
(1-Aminomethyl-3,3-diethyl-cyclobutyl)-acetic acid;
(1-Aminomethyl-3,3-diisopropyl-cyclobutyl)-acetic acid;
(1-Aminomethyl-3,3-di-tert-butyl-cyclobutyl)-acetic acid;
(1-Aminomethyl-3,3-diphenyl-cyclobutyl)-acetic acid;

(1-Aminomethyl-3,3-dibenzyl-cyclobutyl)-acetic acid;

(1-Aminomethyl-2,2,4,4-tetramethyl-cyclobutyl)-acetic acid;

(1-Aminomethyl-2,2,3,3,4,4-hexamethyl-cyclobutyl)-acetic acid;

(R)-(1-Aminomethyl-2,2-dimethyl-cyclobutyl)-acetic acid;

(S)-(1-Aminomethyl-2,2-dimethyl-cyclobutyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-2-methyl-cyclobutyl)-acetic acid;

[1R-(1α,2α,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

(1α,2α,4α)-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;

[1R-(1α,2α,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

(1α,2α,4β)-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-2-methyl-cyclobutyl)-acetic acid;

[1S-(1α,2β,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

(1α,2β,4β)- (1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;

[1S-(1α,2β,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

(1α,2β,4α)-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-2-methyl-cyclobutyl)-acetic acid;

[1R-(1α,2β,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

[1R-(1α,2β,4β)]-(1-Aminomethyl-2-ethyl-4-methyl-cyclobutyl)-acetic acid;

[1R-(1α,2β,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

(1α,2β,4α)-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-2-methyl-cyclobutyl)-acetic acid;

[1S-(1α,2α,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

[1S-(1α,2α,3α)]-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;

[1S-(1α,2β,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

(1α,2α,4β)-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;

(3S, 4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid;

(3R, 4R)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid;

(3R, 4R)-(1-Aminomethyl-3,4-diethyl-cyclopentyl)-acetic acid;

(3S, 4S)-(1-Aminomethyl-3,4-diisopropyl-cyclopentyl)-acetic acid;

(3R, 4R)-(1-Aminomethyl-3,4-diisopropyl-cyclopentyl)-acetic acid;

(3S, 4S)-(1-Aminomethyl-3,4-di-tert-butyl-cyclopentyl)-acetic acid;

(3R, 4R)-(1-Aminomethyl-3,4-di-tert-butyl-cyclopentyl)-acetic acid;

(3S, 4S)-(1-Aminomethyl-3,4-diphenyl-cyclopentyl)-acetic acid;

(3R, 4R)-(1-Aminomethyl-3,4-diphenyl-cyclopentyl)-acetic acid;

(3S, 4S)-(1-Aminomethyl-3,4-dibenzyl-cyclopentyl)-acetic acid;

(3R, 4R)-(1-Aminomethyl-3,4-dibenzyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-ethyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-ethyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-ethyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-ethyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-tert-butyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-tert-butyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-tert-butyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-tert-butyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-phenyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-2-methyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-2-methyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-2-methyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-2-methyl-cyclopentyl)-acetic acid;

(R)-(1-Aminomethyl-2,2-dimethyl-cyclopentyl)-acetic acid;

(S)-(1-Aminomethyl-2,2-dimethyl-cyclopentyl)-acetic acid;

(1-Aminomethyl-2,2,5,5-tetramethyl-cyclopentyl)-acetic acid;

(1α,2β,5β)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic acid;

(2R, 5R)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic acid;

(2S, 5S)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic acid;

(1α,2α,5α)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2α,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2β,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2α,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2β,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2α,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2β,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2α,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2β,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2α,4α)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2α,4α)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2α,4β)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2α,4β)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2β,4α)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2β,4α)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2β,4β)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

and

[1S-(1α,2β,4β)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid.

Especially useful as an agent for insomnia and related disorders is (3S, 4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid.

Also, especially useful as an agent for insomnia and related disorders is (3S, 5R)-3-Aminomethyl-5-methyl-octanoic acid.

The term "lower alkyl" is a straight or branched group of from 1 to 4 carbons.

The term "alkyl" is a straight or branched group of from 1 to 6 carbon atoms including but not limited to methyl, ethyl, propyl, n-propyl, isopropyl, butyl, 2-butyl, tert-butyl, pentyl, except as where otherwise stated.

The benzyl and phenyl groups may be unsubstituted or substituted by from 1 to 3 substituents selected from hydroxy, carboxy, carboalkoxy, halogen, CF_3, nitro, alkyl, and alkoxy. Preferred are halogens.

Since amino acids are amphoteric, pharmacologically compatible salts when R is hydrogen can be salts of appropriate inorganic or organic acids, for example, hydrochloric, sulphuric, phosphoric, acetic, oxalic, lactic, citric, malic, salicylic, malonic, maleic, succinic, methanesulfonic acid, and ascorbic. Starting from corresponding hydroxides or carbonates, salts with alkali metals or alkaline earth metals, for example, sodium, potassium, magnesium, or calcium are formed. Salts with quaternary ammonium ions can also be prepared with, for example, the tetramethyl-ammonium ion. The carboxyl group of the amino acids can be esterified by known means.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R(D) or S(L) configuration. The present invention includes all enantiomeric and epimeric forms as well as the appropriate mixtures thereof.

METHODS AND MATERIALS

Methods

Male Sprague-Dawley rats weighing 250 to 360 g were used for the experiment. The rats were kept on a 12:12-hr light/dark cycle (lights on at 0900) at 23 ± 1°C ambient temperature. They had free access water and food during the experiment. Stainless steel jewelry screws for EEG recording were placed over the frontal and parietal cortices. An EMG electrode was implanted in the dorsal neck muscles.

Recording and analyses. After the recovery period (at least 1 week), rats were moved to sleep recording chambers. The rats were allowed relatively unrestricted movement inside the recording cages. A flexible tether connected the electrodes led to an electronic swivel. The leads from the swivel were routed to Grass Model No. 7D polygraphs in an adjacent room for recording EEG and EMG activity. The vigilance states of wakefulness, nonrapid-eye-movement sleep (NREMS), and rapid-eye-movement sleep (REMS) were determined offline in 10 second epochs. The amount of time spent in each vigilance state was calculated every hour and totaled for the 12-hour period postinjection. Drug or vehicle were administered PO just prior to the onset of the light phase of the rat's light/dark cycle. Each rat received a vehicle and one drug dose.

Results

(3S, 4S)-1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid (Compound 1), 3, 10, and 30 mg/kg PO and (3S, 5R)-3-Aminomethyl-5-methyl-octanoic acid (Compound 2), 1, 3, and 20 mg/kg PO significantly increased NREMS in rats during the 12-hour period following injection (Table 1 and

Table 2, respectively). This increase in NREMS sleep in rats is the typical profile demonstrated by agents that are used as sleep-inducing agents in humans (Meltzer L.T. and Serpa K.A., Assessment of hypnotic effects in the rat: Influence of the sleep-awake cycle, *Drug Development Research* 1988;14:151-159; Depoortere H. et al., Hypnotics: Clinical value of pharmaco-EEG methods, *Neuropsychobiology* 1986;16:157-162).

TABLE 1. Compound 1 Increases NREMS Sleep in Rats (N = 8/Treatment)

	Total Minutes (Mean ± SEM) NREMS for 12-Hour Postinjection	
Compound 1 (mg/kg PO)	Vehicle	Drug
3	370 ± 11	401 ± 8*
10	383 ± 8	409 ± 12*
30	371 ± 14	424 ± 6*

* P ≤0.05 vs Vehicle (paired t-test)

TABLE 2. Compound 2 Increases NREMS Sleep in Rats (N = 8/Treatment)

	Total Minutes (Mean ± SEM) NREMS for 12-Hour Postinjection	
Compound 2 (mg/kg PO)	Vehicle	Drug
1	409 ± 8	432 ± 8*
3	406 ± 9	451 ± 9*
20	412 ± 6	481 ± 6*

* P ≤0.05 vs Vehicle (paired t-test)

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be

obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of formula 1 or 1A or a corresponding pharmaceutically acceptable salt of a compound of formula 1 or 1A.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted, and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection

liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

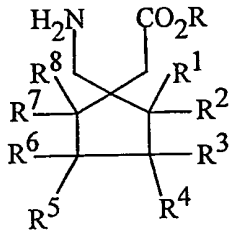
The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 1 g according to the particular application and the potency of the active component. In medical use the drug may be administered three times daily as, for example, capsules of 100 or 300 mg. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 0.01 mg to about 100 mg/kg daily. A daily dose range of about 0.01 mg to about 100 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being

employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

CLAIMS

1. A method of treating sleep disorders in a mammal in need of said treatment comprising administering a therapeutically effective amount of a compound of formula



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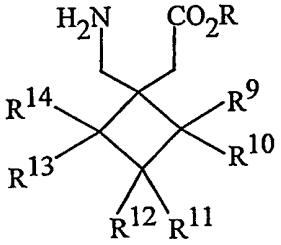
or



1A

or a pharmaceutically acceptable salt thereof wherein:

R is hydrogen or a lower alkyl;

R^1 to R^{14} are each independently selected from hydrogen, straight or branched alkyl of from 1 to 6 carbons, phenyl, benzyl, fluorine, chlorine, bromine, hydroxy, hydroxymethyl, amino, aminomethyl, trifluoromethyl, $-CO_2H$, $-CO_2R^{15}$, $-CH_2CO_2H$, $-CH_2CO_2R^{15}$, $-OR^{15}$ wherein R^{15} is a straight or branched alkyl of from 1 to 6 carbons, phenyl, or benzyl, and R^1 to R^8 are not simultaneously hydrogen.

2. A method according to Claim 1 wherein R^1 to R^{14} are selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl straight or branched, phenyl, or benzyl.

3. A method according to Claim 1 wherein R^1 to R^{14} are selected from hydrogen, methyl, ethyl, or benzyl.

4. A method according to Claim 1 wherein the compound administered is selected from:

(±)-(trans)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid hydrochloride;

(1-Aminomethyl-cyclobutyl)-acetic acid hydrochloride;

(cis/trans)-(3R)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride;

(cis/trans)-(1-Aminomethyl-3-benzyl-cyclobutyl)-acetic acid hydrochloride;

(±)-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-acetic acid hydrochloride; and

(cis)-(3R)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride.

5. A method according to Claim 1 wherein the compound administered is selected from:

(1α,3α,4α)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid;

(1α,3α,4α)-(1-Aminomethyl-3,4-diethyl-cyclopentyl)-acetic acid;

(1α,3α,4α)-(1-Aminomethyl-3,4-diisopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-ethyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-ethyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-isopropyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-isopropyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

(1α,3α,4α)-(1-Aminomethyl-3,4-di-tert-butyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4α)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4α)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;

(S)-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-acetic acid;

(S)-(1-Aminomethyl-3,3-diethyl-cyclopentyl)-acetic acid;

(1-Aminomethyl-3,3,4,4-tetramethyl-cyclopentyl)-acetic acid;

(1-Aminomethyl-3,3,4,4-tetraethyl-cyclopentyl)-acetic acid;

(1α,3β,4β)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid;

(1α,3β,4β)-(1-Aminomethyl-3,4-diethyl-cyclopentyl)-acetic acid;

(1α,3β,4β)-(1-Aminomethyl-3,4-diisopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-ethyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-ethyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-isopropyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-isopropyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-tert-butyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-tert-butyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

(1α,3β,4β)-(1-Aminomethyl-3,4-di-tert-butyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4β)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-3-isopropyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-3-tert-butyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-3-phenyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-3-benzyl-cyclopentyl)-acetic acid;

(R)-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-acetic acid;

(R)-(1-Aminomethyl-3,3-diethyl-cyclopentyl)-acetic acid;

cis-(1-Aminomethyl-3-methyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-ethyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-isopropyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-tert-butyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-phenyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-benzyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-methyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-ethyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-isopropyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-tert-butyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-phenyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-benzyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-ethyl-3-methyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-isopropyl-3-methyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-tert-butyl-3-methyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-methyl-3-phenyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-benzyl-3-methyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-ethyl-3-methyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-isopropyl-3-methyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-tert-butyl-3-methyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-methyl-3-phenyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-benzyl-3-methyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-ethyl-3-isopropyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-tert-butyl-3-ethyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-ethyl-3-phenyl-cyclobutyl)-acetic acid;
cis-(1-Aminomethyl-3-benzyl-3-ethyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-ethyl-3-isopropyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-tert-butyl-3-ethyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-ethyl-3-phenyl-cyclobutyl)-acetic acid;
trans-(1-Aminomethyl-3-benzyl-3-ethyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-tert-butyl-3-isopropyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-isopropyl-3-phenyl-cyclobutyl)-acetic acid;

trans-(1-Aminomethyl-3-benzyl-3-isopropyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-tert-butyl-3-phenyl-cyclobutyl)-acetic acid;

trans-(1-Aminomethyl-3-benzyl-3-tert-butyl-cyclobutyl)-acetic acid;

trans-(1-Aminomethyl-3-tert-butyl-3-isopropyl-cyclobutyl)-acetic acid;

trans-(1-Aminomethyl-3-isopropyl-3-phenyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-benzyl-3-isopropyl-cyclobutyl)-acetic acid;

trans-(1-Aminomethyl-3-tert-butyl-3-phenyl-cyclobutyl)-acetic acid;

cis-(1-Aminomethyl-3-benzyl-3-tert-butyl-cyclobutyl)-acetic acid;

(1-Aminomethyl-3,3-dimethyl-cyclobutyl)-acetic acid;

(1-Aminomethyl-3,3-diethyl-cyclobutyl)-acetic acid;

(1-Aminomethyl-3,3-diisopropyl-cyclobutyl)-acetic acid;

(1-Aminomethyl-3,3-di-tert-butyl-cyclobutyl)-acetic acid;

(1-Aminomethyl-3,3-diphenyl-cyclobutyl)-acetic acid;

(1-Aminomethyl-3,3-dibenzyl-cyclobutyl)-acetic acid;

(1-Aminomethyl-2,2,4,4-tetramethyl-cyclobutyl)-acetic acid;

(1-Aminomethyl-2,2,3,3,4,4-hexamethyl-cyclobutyl)-acetic acid;

(R)-(1-Aminomethyl-2,2-dimethyl-cyclobutyl)-acetic acid;

(S)-(1-Aminomethyl-2,2-dimethyl-cyclobutyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-2-methyl-cyclobutyl)-acetic acid;

[1R-(1α,2α,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

(1α,2α,4α)-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;

[1R-(1α,2α,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

(1α,2α,4β)-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-2-methyl-cyclobutyl)-acetic acid;

[1S-(1α,2β,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

(1α,2β,4β)- (1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;

[1S-(1α,2β,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

(1α,2β,4α)-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-2-methyl-cyclobutyl)-acetic acid;

[1R-(1α,2β,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

[1R-(1α,2β,4β)]-(1-Aminomethyl-2-ethyl-4-methyl-cyclobutyl)-acetic acid;

[1R-(1α,2β,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

(1α,2β,4α)-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-2-methyl-cyclobutyl)-acetic acid;

[1S-(1α,2α,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

[1S-(1α,2α,3α)]-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;

[1S-(1α,2β,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclobutyl)-acetic acid;

(1α,2α,4β)-(1-Aminomethyl-2,4-dimethyl-cyclobutyl)-acetic acid;

(3R, 4R)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid;

(3S, 4S)-(1-Aminomethyl-3,4-diethyl-cyclopentyl)-acetic acid;

(3R, 4R)-(1-Aminomethyl-3,4-diethyl-cyclopentyl)-acetic acid;

(3S, 4S)-(1-Aminomethyl-3,4-diisopropyl-cyclopentyl)-acetic acid;

(3R, 4R)-(1-Aminomethyl-3,4-diisopropyl-cyclopentyl)-acetic acid;

(3S, 4S)-(1-Aminomethyl-3,4-di-tert-butyl-cyclopentyl)-acetic acid;

(3R, 4R)-(1-Aminomethyl-3,4-di-tert-butyl-cyclopentyl)-acetic acid;

(3S, 4S)-(1-Aminomethyl-3,4-diphenyl-cyclopentyl)-acetic acid;

(3R, 4R)-(1-Aminomethyl-3,4-diphenyl-cyclopentyl)-acetic acid;

(3S, 4S)-(1-Aminomethyl-3,4-dibenzyl-cyclopentyl)-acetic acid;

(3R, 4R)-(1-Aminomethyl-3,4-dibenzyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4β)]-(1-Aminomethyl-3-methyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-methyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-methyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-ethyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-tert-butyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-ethyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-ethyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-ethyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-ethyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-ethyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-tert-butyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-isopropyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-isopropyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-isopropyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-tert-butyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-tert-butyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-tert-butyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-tert-butyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-tert-butyl-cyclopentyl)-acetic acid;

[1S-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-phenyl-cyclopentyl)-acetic acid;

[1R-(1α,3α,4β)]-(1-Aminomethyl-3-benzyl-4-phenyl-cyclopentyl)-acetic acid;

[1S-(1α,3β,4α)]-(1-Aminomethyl-3-benzyl-4-phenyl-cyclopentyl)-acetic acid;

(1R-cis)-(1-Aminomethyl-2-methyl-cyclopentyl)-acetic acid;

(1S-cis)-(1-Aminomethyl-2-methyl-cyclopentyl)-acetic acid;

(1R-trans)-(1-Aminomethyl-2-methyl-cyclopentyl)-acetic acid;

(1S-trans)-(1-Aminomethyl-2-methyl-cyclopentyl)-acetic acid;

(R)-(1-Aminomethyl-2,2-dimethyl-cyclopentyl)-acetic acid;

(S)-(1-Aminomethyl-2,2-dimethyl-cyclopentyl)-acetic acid;

(1-Aminomethyl-2,2,5,5-tetramethyl-cyclopentyl)-acetic acid;

(1α,2β,5β)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic acid;

(2R, 5R)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic acid;

(2S, 5S)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic acid;

(1α,2α,5α)-(1-Aminomethyl-2,5-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2α,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2β,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2α,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2β,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2α,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2β,3α)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2α,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2β,3β)]-(1-Aminomethyl-2,3-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2α,4α)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2α,4α)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2α,4β)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2α,4β)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2β,4α)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1S-(1α,2β,4α)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid;

[1R-(1α,2β,4β)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid; and

[1S-(1α,2β,4β)]-(1-Aminomethyl-2,4-dimethyl-cyclopentyl)-acetic acid.

6. A method according to Claim 1 wherein the compound administered is named (3S, 4S)-1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid.

7. A method according to Claim 1 wherein the compound administered is named (3S, 5R)-3-Aminomethyl-5-methyl-octanoic acid.

8. A method according to Claim 1 wherein the sleep disorder is insomnia.

9. A method according to Claim 1 wherein the sleep disorder is insomnia, and the compound administered is named (3S, 4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid.

10. A method according to Claim 1 wherein the sleep disorder is insomnia, and the compound administered is named (3S, 5R)-3-Aminomethyl-5-methyl-octanoic acid.

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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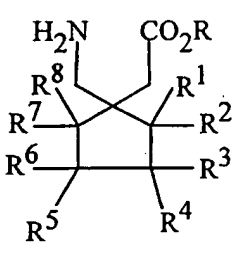
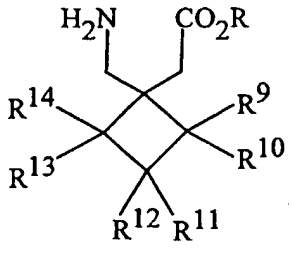
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/000209 A3

(54) Title: GABAPENTIN ANALOGUES FOR SLEEP DISORDERS



(I)



(IA)

(57) Abstract: The invention provides a new use of compounds for formula (I) or (IA) or a pharmaceutically acceptable salt thereof. The compounds are useful in the treatment of insomnia and related disorders.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/16343

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/215 A61K31/197 A61P25/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, MEDLINE, EMBASE, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	WO 00 02546 A (SEGAL CATHERINE A ;WARNER LAMBERT CO (US); MAGNUS MILLER LESLIE (U) 20 January 2000 (2000-01-20) abstract page 2, line 27 -page 7, line 4; claims 1,2 ---	1-6,8,9
Y	WO 99 21824 A (BRYANS JUSTIN STEPHEN ;HORWELL DAVID CHRISTOPHER (GB); WARNER LAMB) 6 May 1999 (1999-05-06) the whole document --- -/--	1-6,8,9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 August 2002	05/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	A. Jakobs

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/16343

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
E	WO 01 42190 A (BLAKEMORE DAVID CLIVE ;BRYANS JUSTIN STEPHEN (GB); WILLIAMS SOPHIE) 14 June 2001 (2001-06-14) abstract page 4, line 26 -page 6, line 4 page 95, line 20 -page 104, line 20; claims 32-43,51; example 1 -----	1-6,8,9

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/16343

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-6,8,9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 7,10
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 7,10

The compound of claims 7,10 does not fall within the scope of claim 1 and has not been searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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